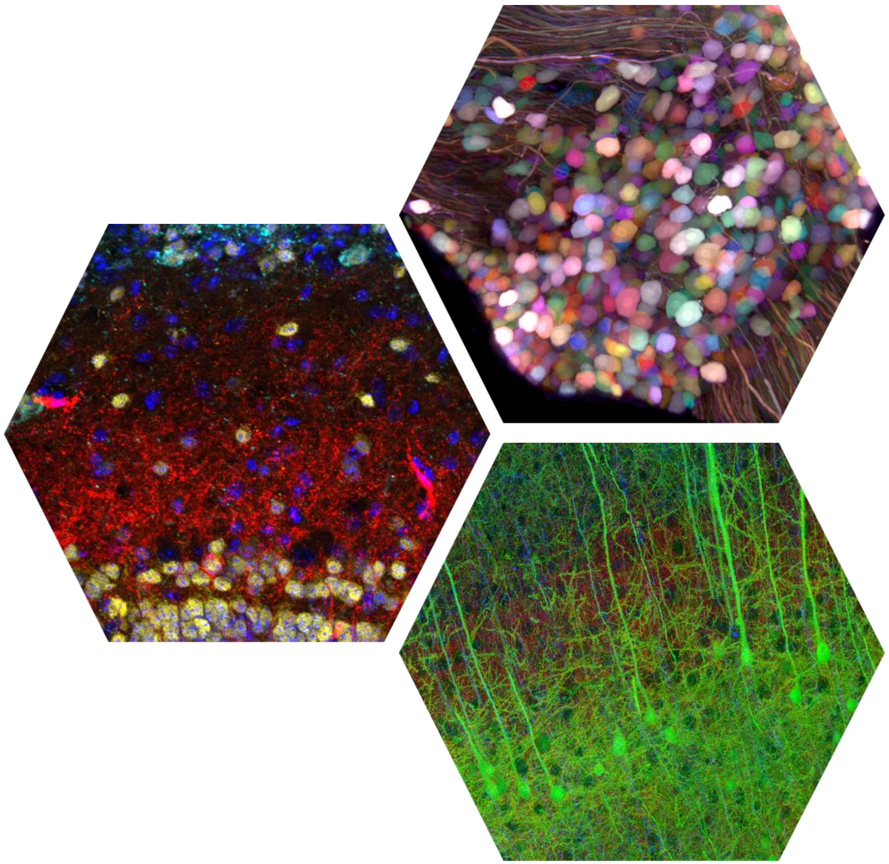
Presentation to the Advisory Committee to the NIH Director



NIH The BRAIN Initiative®

From Cells to Circuits, Toward Cures

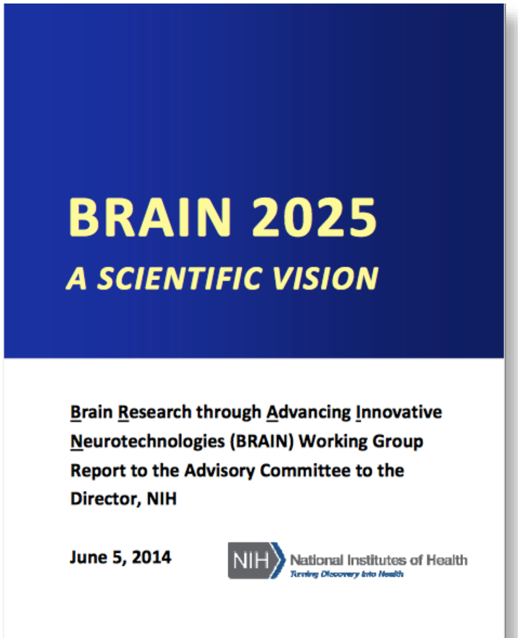
Catherine Dulac, Ph.D.

John Maunsell, Ph.D.

Co-Chairs

June 14, 2019

A focus on circuits and networks



BRAIN 2025

A SCIENTIFIC VISION

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Working Group Report to the Advisory Committee to the Director, NIH

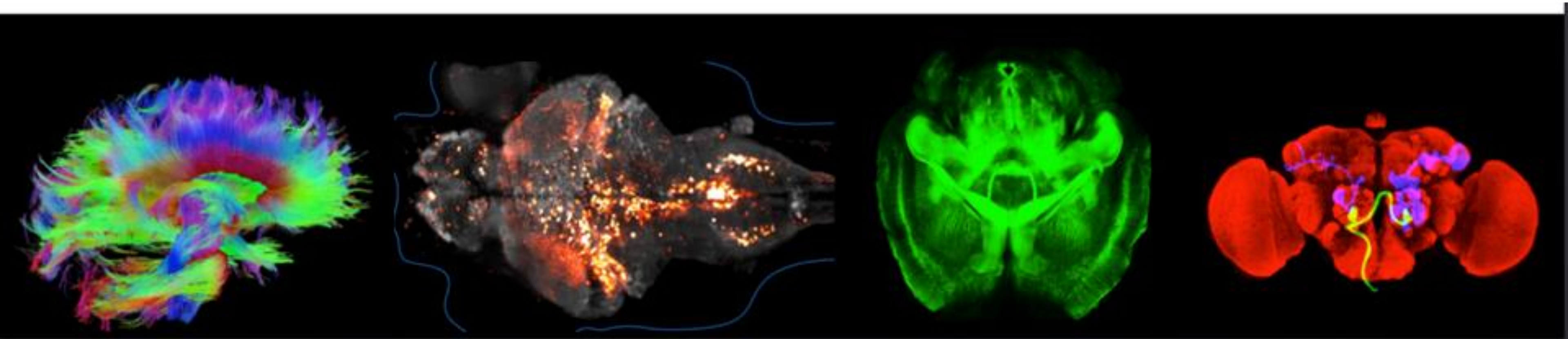
June 5, 2014

NIH National Institutes of Health

"The challenge is to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understand how their interplay creates our unique cognitive and behavioral capabilities."

BRAIN 2025

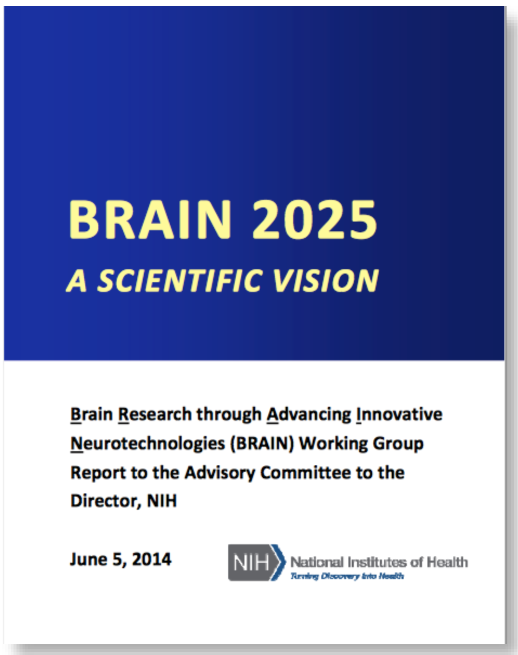
(June 2014)



Presentation Outline

- Charge and Process
- Recommendations
- Summary

Charge to Working Group 2.0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Turning Discovery Into Health

- **Review** BRAIN Initiative activities and progress
- Suggest **tune-ups** to specific goals based on the evolving scientific landscape
- Identify **new opportunities** for research and technology development as well as large **transformative projects**
- Consider opportunities to **train, empower** and **diversify** a broader neuroscience research community

Working Group Roster

- **Catherine Dulac (Co-Chair),** Harvard
- **John Maunsell (Co-Chair),** U Chicago
- **David Anderson**, Caltech
- **Polina Anikeeva**, MIT
- **Paola Arlotta**, Harvard
- **Anne Churchland**, CSHL
- **Karl Deisseroth**, Stanford
- **Tim Denison**, Oxford
- **Kafui Dzirasa**, Duke U
- **Adrienne Fairhall**, U Washington
- **Elizabeth Hillman**, Columbia
- **Lisa Monteggia,** Vanderbilt
- **Bruce Rosen, MGH**
- **Krishna Shenoy, Stanford**
- **Doris Tsao, Caltech**
- **Huda Zoghbi, Baylor**

Ex Officio:

- **James Deshler, NSF**
- **Alfred Emondi, DARPA**
- **Christine Grady, Bioethics, NIH**
- **Lyric Jorgenson, NIH**
- **David Markowitz, IARPA**
- **Carlos Peña, FDA**

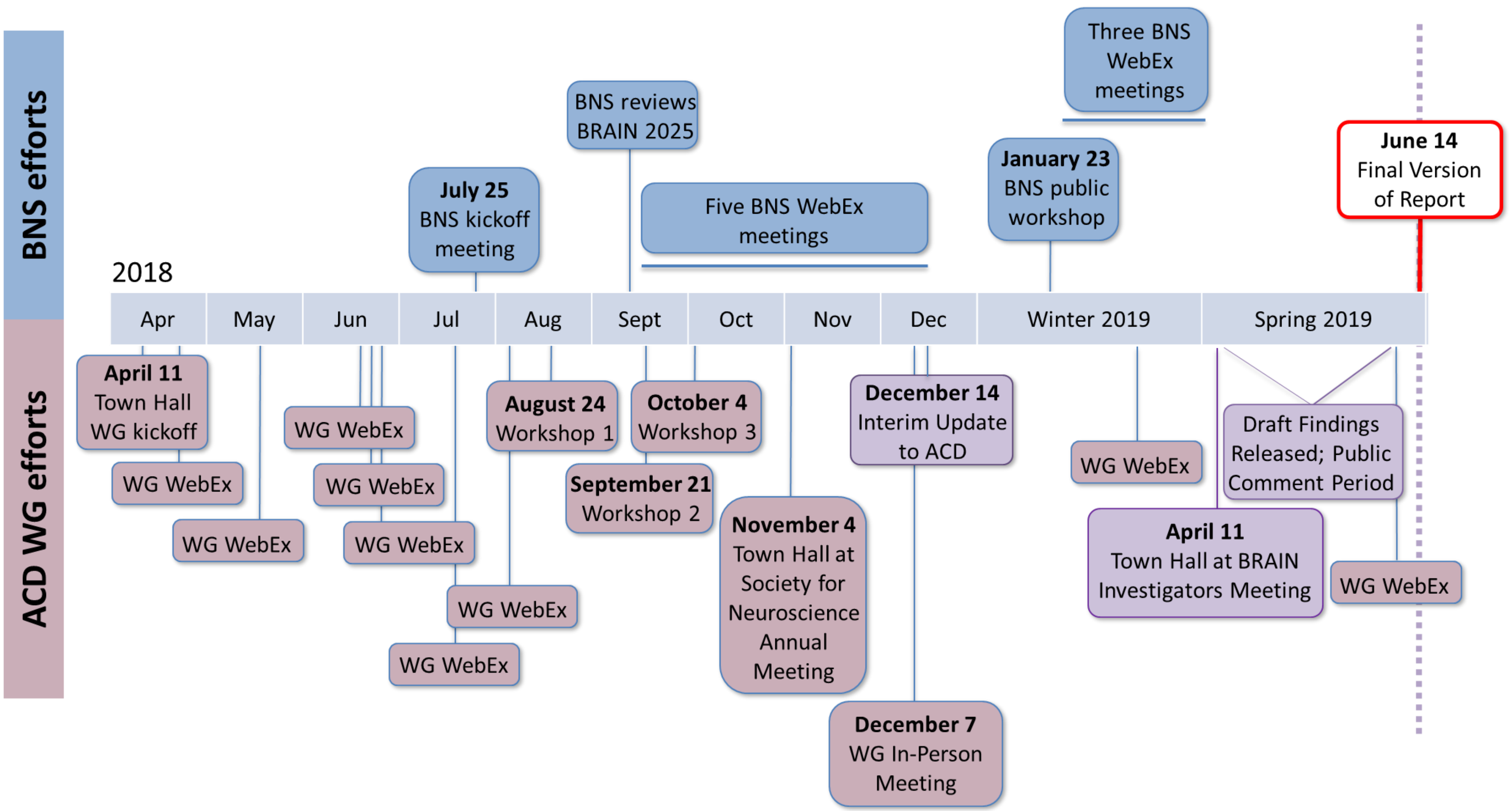
Executive Secretary
Samantha White, NINDS

Science Committee Specialist
Nina Hsu, NINDS

Science Writer
Alison Davis

BRAIN 2025 2.0: Timeline

Timeline for NIH ACD BRAIN Initiative WG:



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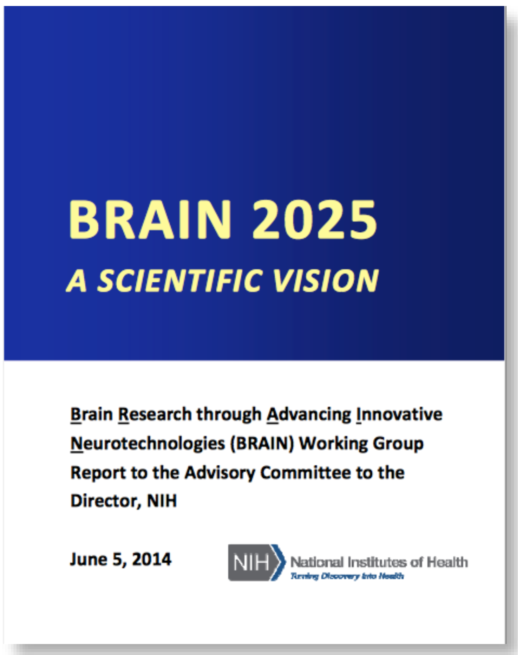
Impressions Thus Far

The roll-out of the BRAIN Initiative 2014-2018

- Faithful to *BRAIN 2025*
- Well-crafted execution
- Thoughtful strategic efforts from NIH program staff
- Largely fulfilling, sometimes surpassing, the initial vision
- Opportunities for refinements & enhancement

BRAIN 2025 Seven Priorities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Turning Discovery Into Health

1. Discovering diversity (cell types)
2. Maps at multiple scales (circuit analyses)
3. The brain in action (monitoring neural activity)
4. Demonstrating causality (precise interventional tools)
5. Identifying fundamental principles (theory and data-analysis tools)
6. Advancing human neuroscience
7. From BRAIN Initiative to the brain (integrative approaches)
8. *[Organization of Science: BRAIN 2.0]*

1. Discovering Diversity

- **Goal:** generate a master "parts list" and taxonomy of brain cell types
- Progress has been **faster than anticipated**, enabled by advances in high-throughput technologies and analytical methods
- **Gaps and Opportunities**
  - Develop/exploit technology to **integrate multimodal** properties of cell types and **develop theory**
  - Develop widely applicable, effective, **cell type targeting methods**
  - Generate a **protein-based understanding** and gain protein-based **access** to cell types
- **Metrics of Success:**
  - Uncover the **role** of specific cell types in circuit function and disease states
  - Determine whether cell types are a **fundamental unit of etiology and pathophysiology**, and whether they may be potential **targets for therapies** in human brain disorders

2. Maps at Multiple Scales

- **Goal:** reconstruct the anatomy of brain circuits at all scales
- **Substantial progress,** reflected by impressive improvements in **tissue processing and imaging** that are bringing more precision to the study of brain regions and circuitry
- **Gaps and Opportunities**
  - Increase the speed of **tissue clearing, labeling, imaging and analysis** for large brain regions and whole brains
  - Improv**e multi-scale observations** that merge structure and function and include **non-neural cell types**
  - Improve functional MRI resolution to **better than 0.01 mm^3** and invest in **MRI alternatives**
- **Metrics of Success:**
  - Allow a **detailed multiscale** understanding of the structure of the brain in relationship to its numerous functions
  - Understanding **how changes in connectivity lead to aberrant function** and new avenues for **diagnostic** and **therapeutic approaches**

3. Brain in Action

- **Goals:** recording neuronal activity in behaving animals to determine what signals are encoded and how they change according to state/context
- **Good progress**, driven in part by **improvements in experimental devices** that integrate electrophysiology with optical imaging, optogenetics, and pharmacologic modulation
- **Gaps and Opportunities**
  - **Expand functionality and integration** of optical, electrophysiological and neurochemical methods
  - Capitalize upon **machine learning** based data analyses
  - Improve tools for studying primate brains, including **technologies beyond fMRI**
  - Develop tools to measure **synaptic strength** and **neuromodulation**
- **Metric of Success:**
  - Data extensive and precise enough to generate and test new theories on **how integrated circuit activity generates perception and behavior**

4. Demonstrating Causality

- **Goals:** use interventional strategies to test cause-and-effect relationships between structure and function
- **Considerable progress**, with major short- and long-term goals in the process of being completed
- **Gaps and Opportunities**
  - **Advance the scale** of multiple single-cell perturbation by 10-fold per year and develop methods for precise single cell activity manipulation **in mobile animals and deep structures**
  - Define the **minimal** number of individually specified neurons needed to alter specific behaviors
  - Apply **nanomaterial-based technology** for neural interrogation and circuit dissection
- **Metrics of Success:**
  - Integrated neurotechnologies to modulate activity throughout the brain and **produce predictable outcomes**
  - Define causal circuits for **selected behaviors** as well as **maladaptive behavioral disorders**

5. Identifying Fundamental Principles

- **Goal:** help organize experimental observations into conceptual frameworks and build predictive models from these frameworks
- **Good progress, but continued emphasis needed**, stimulating development of new approaches to deepen understanding of motor control, decision-making, and other brain functions
- **Gaps and Opportunities**
  - **Foster interactions** between experimentation and theory
  - Continue development of **novel and diverse theoretical frameworks and data analysis** and **bridge micro- and macro-scales**
  - **Integrate** cell type specific information into network models
  - Expand and broaden **training and recruitment** of quantitative expertise.
- **Metrics of Success:**
  - **Maturation of an alliance** between experimental and theoretical neuroscience comparable to those in the physical sciences
  - Identify **general principles** of brain function applicable **across scales**

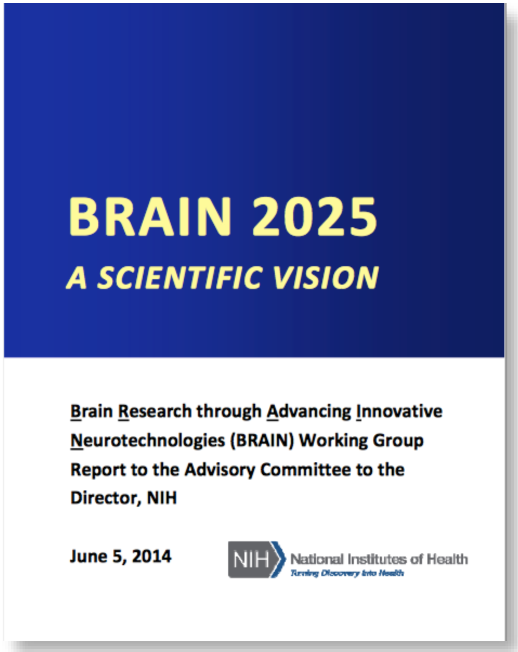
6. Advancing Human Neuroscience

- **Goal:** explore the function of the human brain in ways that will translate new discoveries and technologies into effective diagnosis prevention and treatment of nervous system disorders
- **Poised for progress during BRAIN 2.0**
- **Gaps and Opportunities**
  - Develop **better invasive and noninvasive tools** to observe, manipulate and understand human brain function
  - **Integrate data and meta-data** from genetic, imaging, physiology, and brain-modulation studies
  - Form **collaborative networks** around fundamental and translational human neuroscience research and **increase coordination** of data collection, sharing, and dissemination
  - **Train** clinical investigators, scientists, and physician scientists in team-based human neuroscience
- **Metric of Success:** Advances in this area are the **heart of BRAIN**, revealing mysteries of humans' unique cognitive abilities and helping us treat or prevent devastating consequences of brain dysfunction

7. Integrative Approaches

- **Goal:** integrate technology and experimental insights generated by work in the different Priority Areas
- **Integration is critical**: We expect Priority Area 7 will see substantial growth during BRAIN 2.0
- **Gaps and Opportunities**
  - Connectivity and functional maps at **multiple scales** that retain **cell-type information**
  - Integration of **electrophysiological** and **neurochemical** methods
  - Integration of **perturbational** techniques with other technologies
  - Tools to integrate **molecular, connectivity, and physiological** properties of **cell types**
- **Metric of Success:**
  - Integration of multiple advanced neurotechnologies to **achieve "a sum greater than the parts"** will advance understanding of complex brain functions such as perception, emotion and motivation, cognition and memory, and action, and inspire new cures for brain dysfunction

BRAIN 2025 Vision and 7 Priorities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8. ***[Organization of Science: BRAIN 2.0]***

Organization of Science: Data Sharing

- **Goal:** BRAIN Initiative productivity will increase as a result of widespread sharing of developed technologies and knowledge.
- **Gaps and Opportunities**
  - Data from BRAIN Initiative-funded projects **must be shared publicly** upon first publication in a peer-reviewed journal
  - **Assign credit** to those who collect the data
  - Data should be **stored in standardized formats**: e.g., *Neurodata Without Borders* in systems neuroscience
  - **Data should be FAIR** (findable, accessible, interoperable, and reusable)
- **Metric of Success:**
  - Adoption and enforcement of the NIH BRAIN Initiative data-sharing policy will extend value from individual datasets by enabling re-use and promotes higher standards for data management and curation

Notice of Data Sharing Policy for the BRAIN Initiative:
https://grants.nih.gov/grants/guide/notice-files/NOT-MH-19-010.html

Organization of Science: Human Capital

- **Goal:** foster close interactions among researchers from a broad range of fields and backgrounds to multiply BRAIN Initiative investment
- **Gaps and Opportunities**
  - **Enhance diversity** in the BRAIN Initiative-funded workforce by supporting students, postdocs and investigators from diverse backgrounds, including from groups under-represented in health-related research
  - Attract **quantitative expertise** to neuroscience
  - **Consciously balance individual-investigator research with team science -** both are vital for advancing our understanding of the brain
  - More **clinical and translational expertise** is needed to achieve bold outcomes envisioned for BRAIN 2.0
  - Consider approaches to **support training** across industrial and academic sector
  - Consider adding **additional neuroethics training** opportunities within existing responsible conduct of research training requirements

Organization of Science: Sharing and Using BRAIN Technology

- **Goal:** strategic investment to facilitate rapid, efficient and effective collaborative dissemination of techniques from innovators to end users
- **Gaps and Opportunities**
  - **Translation council** to advise on supporting dissemination from the portfolio of NIH BRAIN Initiative technologies
  - **Training boot camp** for entrepreneurial academic scientists to help them identify the most suitable dissemination model
  - Strengthen a **culture of close collaboration** between innovators and end users
- **Metric of Success:**
  - A much broader community of neuroscientists will have ready access to the latest technology

Public Engagement
From BRAIN to Brain Disorders

- **Public Engagement:**
  - **Public input** must guide the BRAIN Initiative research enterprise
  - **Barriers** that prevent inclusion in human research must be actively addressed
  - **Recruiting** a new generation of neuroscientists. Outreach to high school students and the general public
- **Bringing NIH BRAIN Initiative advances to brain disorders**
  - **List funding opportunities outside of the NIH BRAIN Initiative** that have resulted from its investment to attract researchers to related funding opportunities
  - Leverage the ***All of Us Research Program*** to recruit participants for human neuroscience research

Transformative Projects

Large-scale projects that will yield particularly important resources and data to propel neuroscience far into the future:

- **A Cell Type-Specific Framework for Understanding Brain Function and Dysfunction**: generate and implement methods to access, manipulate and model clinically-relevant cell types across species
- **The Human Cell Atlas:** generate an anatomically informed, highly granular cell census of the whole human brain
- **The Mouse Brain Connectome**: comprehensively map the entire mouse brain, enabling study of brain circuitry from synapses to coordinated function and behavior
- **Reaching Circuit Cures:** achieve circuit-level understanding of, and interventions for, a vulnerable circuit as a move toward protecting or correcting a major human neuropsychiatric disease symptom
- **Memory and the Offline Brain:** learn how the brain retrieves and leverages information from internal models and memory systems

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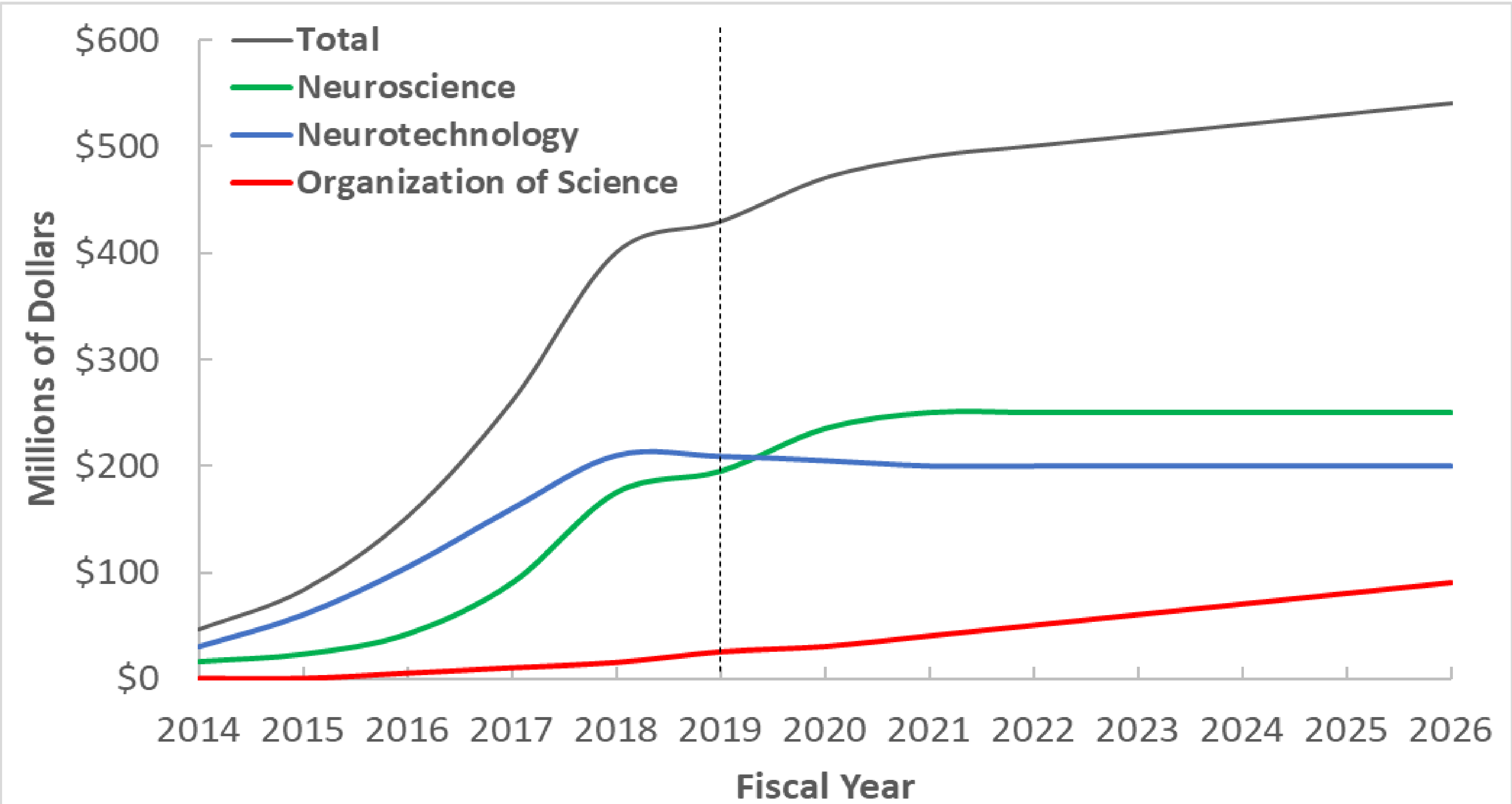
Major Finding and Proposed Funding Strategy

- **Stay on the productive path already underway** for the NIH BRAIN Initiative, continuing support for technology development and targeted study of circuit components



Major Findings

- **Stay on the productive path already underway** for the NIH BRAIN Initiative, continuing support for technology development and targeted study of circuit components
- Added emphasis on **behavior** paradigms and quantitative analysis, **subcortical** structures, **model organisms**
- Encourage BRAIN 2.0 to **consciously balance individual-investigator research with team science** – as both levels of inquiry are vital for advancing our understanding of the brain
- Devote ample BRAIN Initiative resources to large-scale **transformative projects**

The BRAIN Initiative®

Thank You!

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